Biomarkers of Potential Harmful Effects[a,b]
Table 5-4

Bronchioalveolar lavage response	Inflammatory cells, protein, cytokines	Yes	Yes	Yes	No	No	NDA	Provides different types of data with single procedure	Bronchoscopy is too invasive for large epidemiological studies
	Neutrophil elastase α1-antiprotease complex	Yes	Yes	Yes	No	No	NDA	Provides different types of data with single procedure	Bronchoscopy is too invasive for large epidemiological studies
	α1-antitrypsin	No	No	Yes	Yes	Yes	NDA	May be specific to tobacco smoke	Requires invasive test; short half-life
Inflammatory mediators of response	Leukotrienes	Yes	NDA	No	Yes	No	NDA	May be measured in urine, bronchioalveolar lavage, and serum	Substantial number of confounders
Pulmonary function tests	FEV1, FVC	Yes	Yes	Yes	No	No	Yes	Widely available	Low sensitivity for mild disease. Decrease in function with aging. Large interindividual variation
Periodontal disease	Periodontal height	Yes	Yes	Yes	No	No	Yes		
	Gum bleeding	Yes	Yes	Yes	No	No	Yes		
Osteoporosis	Fractures	Yes	NDA	NA	No	No	Yes	Easily measured	Numerous confounders
	Bone density	NDA	NDA	Yes	No	No	Yes		
Skin	Premature wrinkling	Yes	NDA	NA	No	No	NA		Lack of specificity; involves subjective evaluation
Fetal and neonatal effects	Birth weight	Yes	Yes	Yes	No	No	Yes	Data collection is easy	Nonspecific; numerous confounders
Weight	Weight loss and gain	Yes	Yes	Yes	No	No	Yes	Both a biomarker for metabolism and an important outcome for some people.	Some people perceive weight loss as a benefit of smoking, despite significant adverse effects associated with smoking

NOTE: NA = not applicable; NDA = no data available; FVC = Forced vital capacity; FEV_1 = Forced expiratory volume in 1 sec; HDL= high-density lipoprotein; LDL = low-density lipoprotein.
[a]Selected examples; list is not all-inclusive.
[b]References are not provided in this table but can be found in the text of this and disease-related chapters.
[c]Any report related to a disease outcome associated with tobacco where the report is plausible but has not necessarily been replicated.

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Biomarkers of Potential Harmful Effects[a,b]
Table 5-4

Category	Variables Used in Literature	Dose-Response Data	Associated with Cessation or Half-life	Target Tissue Assay Available	Chemical Specificity	Specific to Tobacco	Related to a Disease Risk[c]	Strengths	Limitations
Enzymatic induction	Aryl hydrocarbon hydroxylase	No	>30 d	Yes	Yes	No	Yes	Indicates acquired changes in susceptibility; related to DNA–adduct levels	Technically difficult to assess in large epidemiological studies.
	CYP1A2	No	NDA	Yes	Yes	No	Yes	Indicates acquired changes in susceptibility; related to DNA–adduct levels	Technically difficult to assess in large epidemiological studies
	DNA repair enzymes	NDA	Yes	Yes	NA	No	NDA	Indicates acquired changes in susceptibility; provides analysis of what is likely to be critical part of carcinogenesis	Technically difficult
	Microarray assays for mRNA expression and proteomics	NDA	NDA	Yes	NA	No	NDA	Reflects integrated measure of multiple genotypes, provides complex data potentially usable for rapid identification of important risk factors	Difficult to perform; relationship to disease risk is technically difficult to prove; requires extensive laboratory validation; RNA and protein microarray assays are expensive; large-scale studies are needed; Refined bioinformatic analysis required
Chromosomal alterations	Chromosomal aberrations	Yes	Yes	Yes	No	No	Yes	Can be done in blood as surrogate tissue. Similar lesions observed in cancer. Can be measured in persons without cancer	Very nonspecific; relationship to target organ is not established; significant lack of specificity and wide overlap between smokers and nonsmokers
	Micronuclei	Yes	Yes	Yes	No	No	NDA	Facile assay	Lack of specificity
	Sister chromatid exchanges	Yes	Yes	No	No	No	No	Easy to do in blood as surrogate tissue. Can be measured in persons without cancer	Very nonspecific; relationship to target organ is not established; predictivity for disease risk not established. Association with cancer in case-control studies may have case bias. Significant lack of specificity and wide overlap between smokers and nonsmokers
	Loss of heterozygosity	Yes	Yes	Yes	No	No	NDA	Similar lesions observed in cancer	Technically complex; relationship to cancer risk unknown
	Mutations in reporter genes (*HPRT, GPA*)	Yes	Yes	No	No	No	NDA	Facile assay in blood	Relationship to target tissue or blood unknown
	Mutational load in target genes (p53, K-ras)	NA	NDA	Yes	No	No	NDA	Target gene specificity	Very difficult to do in normal tissues
Mitochondrial mutations	Deletions, insertions	NDA	NDA	Yes	No	No	NDA	Provides corroborative marker	Relationship to disease not established

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Biomarkers of Potential Harmful Effects[a,b]
Table 5-4

Epigenetic cancer effects	Whole genome methylation	NDA	NDA	Yes	No	No	No	Facile assay	Relationship to disease unknown
	Hypermethylation of promoter regions	NDA	NDA	Yes	No	No	No	Similar lesions observed in cancers	Technically difficult; relationship to risk unknown
Lipids	Blood lipids: HDL, LDL, oxidized LDL, triglycerides	Yes	NDA	Yes	Yes	No	Yes	May be directly related to disease risk	Levels among heavy smokers cannot be distinguished. Wide interindividual variation. Many individuals under medication therapy. Significant confounders exist
Cardiovascular response	Heart rate, blood pressure	No	Yes	Yes	NA	No	Yes	Easy to measure; intraindividual differences may be important for the individual	Both interindividual and intraindividual differences are significant. Substantial confounders exist, and many persons are on medications
Thrombosis	Bleeding time	No	NDA	Yes	No	No	No	Minimally invasive	Very nonspecific
	Fibrinogen	NDA	NDA	Yes	Yes	No	NDA	Pathogenically related to disease	Does not distinguish levels of smoking. Nicotine might separately affect these parameters so limited use in persons using NRT
	Prothrombin time, partial thromboplastin time, plasminogen activator inhibitor, C-reactive protein	Yes	NDA	Yes		No		Leave a fingerprint at the site of their formation	
	Urinary thromboxane and prostacyclins	Yes	No	No	Yes	No	Yes	May be markers of platelet–vascualr interactions; reflect chronic exposure	Technically difficult. Wide overlap of values due to individual differences in response
	Platelet activation and survival	Yes	NDA	Yes	No	No	No	Platelet activation in vivo might be pathophysiologically related to cardiac artery thrombosis	Technically difficult to use for large numbers of subjects. Significant number of confounding variables. Smoking increases platelet counts
Blood cell parameters	White blood cell counts (i.e., lymphocytes, neutrophils, total counts)	Yes	Yes	Yes	Yes	No	Yes	Can be a surrogate marker for several processes including atherosclerosis and thrombosis	Relationship to disease uncertain, although alterations in levels are linked epidemiologically to disease. Wide interindividual and intraindividual variation and large number of confounders
	Hematocrit, hemoglobin, red blood cell mass	Yes	Yes	Yes	No	No	No	Can reflect both cardiac and respiratory disease risk	Insensitive; wide interindividual differences

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vey methods because of inadequate sample sizes and insufficient representation of various geographic or demographic groups or of the earliest stages of pregnancy. There is a need for surveys devoted specifically to pregnant women in all stages of gestation, irrespective of the receipt of medical care. Survey content should include other known or putative causes of adverse maternal or fetal outcomes, as well as detailed product types and usage patterns. Recommendations for general population surveillance can be found in Chapter 6 of this report.

Biochemical and toxicological exposure measures should be a routine part of surveillance for exposure to conventional products as well as PREPs. These will be necessary to conduct more precise, coordinated toxicological studies and also to assess actual exposure rates more accurately. For example, dose may be measured by maternal serum and urine cotinine levels, which have shown reliable correlations with maternal, and consequently fetal, tobacco smoke exposure. Self-reported data have been found unreliable, since pregnant women tend to underreport tobacco use because of the stigma attached to smoking. Also, self-reports do not adequately account for differences in depth and frequency of puffs among smokers.

OTHER HEALTH EFFECTS (SEE SECTION II, CHAPTER 16)

Feasibility of Harm Reduction in Therapy

Several important diseases and conditions of adults, in addition to cardiovascular diseases, chronic obstructive lung disease and various cancers, have been associated with tobacco use, including—but not limited to—peptic ulcer disease, poor wound healing, inflammatory bowel disease, rheumatoid arthritis, oral disease, dementia, osteoporosis, ocular disease, diabetes, dermatological disease, schizophrenia, and depression (see Chapter 16). Some of these associations are supported by substantial scientific evidence, and a causal linkage is likely. These illnesses must ultimately be subjected to the same evaluation of changing risks and outcomes associated with PREPs, because these are common and clinically important conditions, even if they are not as often fatal as cancer, cardiovascular disease or pulmonary disease. Further, each of the conditions for which the association with tobacco use is substantial also offers the opportunity to address pathogenic mechanisms related to the varying constituents of PREPs, as well as the impact on disease incidence of concomitant behaviors and exposures such as alcohol use, various dietary elements, and certain medications.

Utility of Pre-clinical Studies and Short-term Indicators of Clinical Harm Reduction

Some of the conditions reviewed in this chapter may be applied as indicators of the general biological effects of new tobacco products. For example, cigarette smoking has been consistently found to be an independent risk factor for an adverse clinical course of both peptic ulcer disease and wound healing. The effects of smoking on ulcer formation and healing have been clearly described clinically and in animal models (Ma et al., 1999). Peptic ulcers have been found to be larger, slower to heal, and more likely to recur among smokers and to exhibit clinically improved healing upon cessation (Tatsuta et al., 1987). Surgical and traumatic wounds heal more slowly among cigarette smokers Mosely et al., 1978; Kwaiatkowski et al., 1996). The committee recommends that rigorous clinical studies be designed and executed to determine whether variations in ulcer and wound-healing rates are related to various categories of tobacco products, including those with claims of harm reduction. This may offer the opportunity to define some clinical outcomes that have clinical relevance in their own right and to identify potential

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indicators of harm alteration much sooner after the introduction of PREPs than would be possible when evaluating heart disease and cancer.

Other candidate diseases for such evaluation might include periodontal disease (Bergstrom, 2000; Haber, 1994), Crohn's disease (Rhodes and Thomas; 1994), and rheumatoid arthritis (Uhlig et al., 1999). Here the outcomes to assess would be the effect of various conventional tobacco products and PREPs on the natural history of these conditions, including intermittancy, progression or regression, and longitudinally collected biomarkers of disease severity. As noted above, PREPs that alter the history and outcomes of these conditions could be further evaluated for specific constituent exposures associated with this altered history. This may lead to a more refined understanding of pathogenic mechanisms as well.

Clinical and basic research on intermediate clinical outcomes is also needed. For example, as noted in this chapter, the risk of osteoporosis has also been strongly linked to cigarette smoking. In controlled observational studies, bone mineral density has been found to be significantly lower among cigarette smokers, which contributes to a greater risk of osteoporotic fractures among older populations. While the effects of smoking on fracture rates may take a few decades or longer to detect, it is possible that surveillance of bone mineral density among those using PREPs and conventional products may be informative in a shorter time period and, thus, serve to detect important outcomes over an interval in which tobacco policy and clinical preventive interventions may have their greatest effects.

Surveillance

The committee recommends that selected conditions, as reviewed in this chapter, be part of a comprehensive, population-based surveillance program, outlined in Chapter 6. This will allow determination of the relationship between the use of PREPs and of trends in occurrence for these tobacco-related conditions and assessment on a national basis of whether changes in tobacco product use have an effect on these important health problems. Based on these surveillance findings, more specific population, clinical, and basic research studies can be directed to evaluate PREPs to pursue causal mechanisms and to suggest more effective interventions.

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(Fiore et al., 2000) recommend that "Pharmacotherapy should be considered when a pregnant woman is otherwise unable to quit, and when the likelihood of quitting, with its potential benefits, outweighs the risks of the pharmacotherapy and potential continued smoking".. It is generally thought that NRT can reasonably be used with pregnant patients if prior behavioral modifications have failed and the patient continues smoke at least 10–15 cigarettes per day (ACOG, 1997). There are no data regarding the efficacy of potential reduced-exposure products (PREPs) during pregnancy, but there is the presumption that the tobacco-related PREPs are likely to have adverse effects at some level and that until further evidence is produced, existing guidelines concerning pharmacologic PREPs still pertain.

Clinical Assessment of Tobacco-Related Disease and Utility in a Preclinical Setting

To practically assess the health effects of PREPs, reliable measures of health outcomes that can be utilized in a relatively short time are desired. Among the reproductive outcomes of maternal smoking, intrauterine growth retardation resulting in low-birthweight babies has been studied extensively, and a large body of evidence has supported a causal link with cigarette smoke exposure. The committee recommends, based on currently available scientific knowledge, that fetal birthweight be used as an reliable outcome measure for evaluating the harm reduction potential of specific PREPs. Study designs should include repeated cohort or case-control studies of pregnant women, with an appropriate distribution of exposures to both PREPs and conventional products, and suitable contrast groups. Concomitant, coordinated toxicological studies should be undertaken to provide biological correlations with clinical outcomes. Such outcomes as fetal birth weight and the incidence of other reproductive and developmental health outcomes (e.g. fertility outcomes, placental complications, gestational age at birth, incidence of sudden infant death syndrome [SIDS], spontaneous abortions) should be considered primary objects of study in order to assess the harm reduction potential of specific PREPs.

Findings in pregnant women exposed to PREPs may have value beyond maternal or fetal outcomes. The nature of adverse effects derived from PREP exposure will likely be determined much sooner in this case than findings on chronic disease outcomes in humans, such as various cancers and cardiovascular disease. Should adverse findings become apparent, there may be substantial implications for chronic illnesses among older adults, and coordinated pathogenic studies might allow conclusions on new tobacco product outcomes in advance of studies exploring longer "incubation periods."

The committee recommends that further basic research be undertaken to elucidate the components of cigarette smoke that are primarily responsible for adverse health outcomes. In order to evaluate the safety of many PREPs, it is important to understand the toxicity of specific smoke components, especially nicotine and CO, on the pathogenesis of intrauterine growth retardation, spontaneous abortion, and other health outcomes. In addition, a better understanding of the risks of bupropion SR use by pregnant women (i.e., seizure risk) and the teratogenic effects of nicotine on the central nervous system (CNS) is needed for adequate risk–benefit analysis of the harm reduction potential of these products.

Surveillance of Tobacco Use Patterns Among Pregnant Women

Central to understanding exposure to tobacco products is continuous population information on usage patterns among pregnant women. This may not be attainable by general population sur-

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Clinical Assessment of Tobacco-Related Disease

An alternative is to proceed with interventional trials based on current knowledge if there are uncertainties about the added value of dose–response data or untested biomarkers to study design. As an example, an intervention study of the effect of smoking reduction on COPD could be considered, similar in design to the Lung Health Study (Anthonisen et al., 1994), a large prospective trial of the effects of smoking cessation on rate of decline of FEV_1 (forced expiratory volume at 1 second) in middle-aged smokers with mild COPD. Another approach is to conduct a trial using a low-tar and moderate-nicotine product made available from a noncommercial source to avoid product endorsement issues.

Design of population studies for harm reduction of major respiratory diseases is challenging because of uncertainties about effectiveness and long-term compliance with harm reduction interventions. Reduction in the burden of tobacco-related respiratory diseases through harm reduction strategies should be a major priority for the nation's public health.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS (SEE SECTION II, CHAPTER 15)

Feasibility of Harm Reduction in Therapy

Cigarette smoking is a major cause of fetal and infant morbidity and mortality (USDHHS, 1988 and 1990; Kleinman et al., 1988) . This is particularly true for the associations with low-birthweight and its consequences, as well as preterm delivery and SIDS(Shah and Bracken, 2000; NVSR, 2000; USDHHS, 1983; Leach et al., 1999). For several important adverse reproductive effects of maternal smoking, a decrease in smoking has been found to be associated with a decrease in risks to the fetus and infant (Li et al., 1993; Hebel et al., 1988). The greatest benefit, of course, comes from smoking cessation. However, the smoking cessation rate for women smokers who become pregnant is very low and remain comparable to those in the general population, despite knowledge of the harmful effects of smoking and personal experience with adverse fetal and infant conditions. Moreover, as current rates of smoking increase slowly among adolescent women, these adverse effects associated with tobacco smoke exposure while pregnant are likely to worsen.

Dose-Response Relationship

On average, infants exposed to maternal smoking in utero are 200 grams lighter and 1.4 cm shorter than those unexposed (Wang et al., 1997). A strong dose–response relationship has been supported in numerous studies (Li et al., 1993),and a decrease in dose (number of cigarettes) in controlled studies has led to increased birthweights in a predictable pattern (Wang et al., 1997) . What is known about the mechanism of effect of cigarette smoke on the fetus suggests that several agents in tobacco smoke contribute to the adverse effects. There is evidence that CO plays a major role in growth retardation through increased tissue hypoxia (Benowitz et al., 2000) . Nicotine has also been thought play a role through increasing vasoconstriction and decreasing perfusion through the placenta .

Although nicotine replacement products and buproprion are currently not approved by the Food and Drug Administration for use by pregnant women, the Agency for Healthcare Research and Quality's (AHCRQ) Clinical Practice Guidelines for Treating Tobacco Use and Dependence

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clear need to mitigate the harmful effects of exposure to both mainstream and secondary tobacco smoke. It is generally accepted that cessation of smoking slows or stops the progression of the lung diseases related to smoking and it is plausible that decreasing smoking will reduce the severity of chronic lung diseases and the incidence of respiratory infections. However, there is no adequate scientific evidence to support this because the effects of reduced smoking on harm reduction have not been extensively studied in man.

Dose-Response Relationship

There is a need to determine dose–response relationships more precisely and to develop biomarkers of respiratory disease. Rational design of studies to assess harm reduction requires knowledge of the dose–response relationship. At present, such data for respiratory diseases are limited and of uncertain quality. Study design would also incorporate biomarkers of disease, and the testing of current and new biomarkers might be done concurrently in the models and populations studied for dose-effects. The Cancer Prevention Studies I and II, large-scale prospective studies, however, do suggest a direct dose–response relationship between cigarettes smoked per day and mortality rates from COPD (NIH, 1996 and 1997), indicating that decreasing the number of cigarettes smoked may lead to fewer deaths from COPD.

Biomarkers of Tobacco-Related Disease

There are currently no specific molecular biomarkers of the nonneoplastic respiratory diseases due to smoking tobacco products. No unique molecular or genetic defect specific for tobacco-related respiratory disease has been identified. The processes involved, such as inflammation and increased levels of oxidants, are not unique to tobacco-related respiratory diseases. Identifying unique biomarkers is further confounded by the heterogeneous nature of these diseases, the complex mixture of tobacco smoke, and the range of individual susceptibilities to the harmful effects of tobacco smoke. The most widely used markers of tobacco-related respiratory diseases in population studies are symptom questionnaires and pulmonary function testing . These have well-known limitations of specificity and sensitivity, particularly for detecting the early effects of tobacco smoke on lungs (USDHHS, 1989). Subtle effects of tobacco smoke exposure on the lung can be detected by sampling fluid in the lower respiratory tract via a bronchoscope inserted into the airways, but the significance of these changes for clinically important pulmonary disease has not been established. Newer approaches such as sampling the subjects' urine (Pratico et al., 1998) or exhaled gas (Ichinose et al., 2000) for metabolic products due to tissue injury have the advantage of noninvasive sampling but must be validated. Clearly, the greatest obstacle for rational development of a specific biomarker is the lack of fundamental information on mechanisms of how tobacco smoke exposure causes specific respiratory diseases.

The availability of dose–response data and validated biomarkers may improve the design of contemplated intervention studies and allow greater confidence in the results. However, the time frame for generating dose–response data and testing biomarkers is uncertain. The inclusion of dose–response considerations and biomarkers in the design of clinical trials on reduction of harm from respiratory diseases must also be validated.

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data are available to address such issues across ethnic groups or gender. Acquisition of such information and research on the environmental and genetic factors that condition interindividual variability in exposure–risk relationships are necessary.

Utility in a Preclinical Setting

Studies in cell culture and model systems can afford much needed information on tobacco-related cardiovascular risk. These might include a profiling of gene expression and translation in cardiovascular tissues in response to cigarette smoke, constituents of smoke, and potential harm reduction substituents. These might identify proteins of potential functional relevance to the transduction of cardiovascular risk. Such studies might be coupled with gene inactivation and overexpression studies to address the role of these proteins *in vivo*. Similarly, studies of exposure to cigarette smoke or to discrete constituents of smoke might be deployed to investigate effects on atherosclerosis progression, susceptibility to vascular injury, thrombotic stimuli, graft rejection, cardiovascular development, or endothelial dysfunction in model systems such as mice. Studies of cardiovascular genomics and ultimately proteomics can also be extended to model systems to investigate gene expression and translation in response to exposure to tobacco-related products in vivo. These observations may, in turn, be related to the pattern of gene expression and translation in cardiovascular tissues obtained from cigarette smokers.

Biomarkers of Tobacco-Related Disease

The predominant mechanisms by which cigarette smoking induces cardiovascular injury is unknown. However, small studies in smokers of potentially relevant biomarkers of platelet and vascular activation, lipid peroxidation, and inflammation afford evidence of a dose–response relationship and a decline on quitting. There is even evidence of a signal in individuals exposed to ETS in the case of some of these markers. More mechanism-based clinical studies are required to confirm and expand these findings. Where possible, these should be related to surrogate measurements of cardiovascular function, such as hemodynamics, flow-mediated endothelial function and estimates of plaque progression by ultrasound or electron-beam computerized tomography (EBCT). Furthermore, biomarker studies can usefully be integrated into many studies in model systems as well as studies of clinical outcome to afford their ultimate validation.

Clinical Assessment of Tobacco-Related Disease

The time course of offset of myocardial infarction and stroke in people who stop smoking suggests that cardiovascular disease represents a tractable scenario in which one might evaluate harm reduction strategies. Clearly, the health effects experienced by the individual and the assessment of the impact of such events can occur in a more reasonable time frame than from cancer in which declines in risk from tobacco exposure reduction may only be apparent after years or decades.

NONNEOPLASTIC RESPIRATORY DISEASE (SEE SECTION II, CHAPTER 14)

In evaluating harm reduction strategies for tobacco-related lung disease, three major nonneoplastic respiratory diseases linked to cigarette smoking are considered: COPD, asthma, and respiratory infections. Respiratory diseases are major tobacco-related illnesses, and there is a

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CARDIOVASCULAR DISEASE (SEE SECTION II, CHAPTER 13)

Dose-Response Relationship

Highly informative information on the existence of a dose-response relationship between cigarette exposure and cardiovascular risk comes from many studies such as the CPS-2 (Thun et al., 1997) and Harvard Nurses' Health Studies (Kawachi et al., 1997). In both instances, there is a relationship between the number of cigarettes smoked and the incidence of cardiovascular events. This is illustrated for the incidence of myocardial infarction and stroke. In both cases, the most striking difference is between nonsmokers and individuals who smoke the least number of cigarettes recorded. The relationship becomes somewhat less pronounced as the number of cigarettes smoked per day increases. Interestingly, ex-smokers tend to occupy a space intermediate between nonsmokers and those with the lowest daily smoking frequency.

This dose–response curve prompts several considerations. First, there is no persuasive evidence of a threshold below that a cardiovascular risk does not exist. This observation affirms the primary objective of encouraging smokers to quit completely. Second, the shallow dose–response relationship, with the impression of a plateau, accords with similar observations relating the number of cigarettes smoked and measurements of systemic bioavailability, such as nicotine and cotinine. The same is true of the relationship with CO (Gori and Lynch, 1985). Although this may represent saturation kinetics of nicotine or CO, the most likely explanation is compensation for lower numbers of cigarettes smoked. Thus, the smoker titrates nicotine delivery toward a range of convergence that is reflected by the measurement of nicotine delivery, which in turn, may reflect dose-dependent convergence of the delivery of additional toxic, but unmeasured, constituents of cigarette smoke. The relative contribution of distinct constituents of cigarette smoke to smoking-related cardiovascular morbidity and mortality is unknown. In this regard, the available information is incomplete regarding any differences between the dose–response relationship of filter or low-tar versus high-tar or unfiltered cigarettes.

Feasibility of Harm Reduction in Therapy

There are no data that are directly informative on the issue of harm reduction. Thus, although a dose–response relationship exists for cardiovascular and cerebrovascular events, we do not know if reducing the number of cigarettes smoked results in a quantitative reduction in the risk of these events. However, the intuitively appealing prospect that this is indeed the case is supported by evidence from individuals who quit smoking. Thus, quitting results in a time- dependent reduction in the incidence of myocardial infarction and stroke. The latter is most nicely illustrated by data relating to subarachnoid hemorrhage, which was significantly elevated in women smokers in the Nurses' Health Study. In addition to evidence from such unequivocal clinical events, there is evidence that the increase in biomarkers of oxidant stress, platelet activation, and inflammation (Benowitz et al., 1993), all of potential mechanistic relevance to tobacco-related cardiovascular injury, rapidly falls toward the normal range on quitting cigarettes. The offset kinetics of more functional surrogates, such as endothelial dysfunction, remain to be determined in smokers. In summary, the data from quitters encourage the prospect that a graded reduction in cardiovascular risk and in biomarkers of this risk may accompany a reduction in the number of cigarettes smoked in pursuit of a harm reduction strategy. It is possible, indeed likely, that individuals and perhaps populations, differ in their susceptibility to tobacco-induced cardiovascular risk and, indeed, in their potential benefit from a harm reduction strategy. Data from quitting studies indicate a considerable variance in the rate of offset of risk, which declines with time. No

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duce exposures and how these changes might affect smoking behavior, metabolic activation, enzymatic induction, conjugation, excretion, biologically effective doses (or their validated surrogates), and biomarkers of potential harm. Separately, these studies can assess differences in risk and provide evidence for modifying effects due to genetic susceptibilities, diet, life-style, occupation, and so forth . However, at the current time, no single biomarker or panel of biomarkers can be considered sufficient indicators of cancer risk by themselves, in part because most have not been sufficiently validated . New technologies are offering new opportunities for biomarkers. Thus, a panel of experts will be needed to devise a set of biomarkers that reflect different exposures, biologically effective doses, and pathways for potential harm.

It is clearly possible to assess the effects of PREPs on cancer as the ultimate outcome, and only such studies can provide definitive evidence for the success of a product. However, the long latency for cancer makes these studies infeasible for making such claims today or in the near future. This relatively long latency period for cancer and the slower decline, probably years or decades, in risk from exposure reduction compared to cardiovascular disease and other tobacco-related diseases will have an impact not only on the time frame of PREP assessment and but also on the health effects experienced by and apparent to the individual. Preneoplastic lesions or the identification of harmful effects in single cells might be used as indicators for the carcinogenetic pathway, but the technology to identify these in the general population or large epidemiological studies is not yet available. In such studies, the characterization of smoking history and behavior is well validated for recent exposures but less accurate for assessing lifetime exposure. Also, self-reported smoking history is insufficient to adequately assess risk in the context of PREP assessments, so biomarkers also are needed to assess exposure, biologically effective doses, and potential harm.

Currently, the best approach to assessing PREPs and cancer risk is to focus on lung cancer, because this is the most common cancer and so will provide studies with the greatest statistical power. However, data are sufficient to conclude that there is a risk that the widespread use of PREPs will shift the burden of cancer in the population from one type to another or from cancer to a different disease. Thus, a particular cancer type cannot be the sole indicator for the success of a PREP, and other cancers, diseases, and overall mortality must be evaluated as well.

Many studies of nicotine suggest that nicotine is unlikely to be a cancer-causing agent in humans or, at worst, that its carcinogenicity would be trivial compared to that of other components of tobacco. The consideration of nicotine as a carcinogenic agent, if at all, is trivial compared to the risk of other tobacco constituents.

Some smokeless tobacco products increase the risk of oral cavity cancers, and a dose–response relationship exists . However, the overall risk is lower than for cigarette smoking, and some products, such as Swedish snus, may have no increased risk. It may be considered that such products could be used as PREPs for persons addicted to nicotine, but these products should undergo testing as PREPs using the guidelines and research agenda contained herein.

The effects of PREPs on cancer risk from environmental tobacco smoke (ETS) are uncertain because of the difficulties in measuring reductions in exposure. Also, although there is clearly an increased risk of lung cancer from ETS, the determination of changes in risk from the use of PREPs will require studies of large numbers of people, and smoking is currently in this country prohibited in many places where ETS might have occurred.

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the use of any harm reduction product will likely increase the risk of cancer at some level as long as there is exposure to tobacco carcinogens, in contrast to abstinence, which stops exposure to all tobacco constituents . Nonetheless, reduction in exposure to tobacco smoke and tobacco products to the lowest possible levels may provide some benefit to individual users and to the general population. However, there are insufficient data from which to conclude how much reduction in exposure would yield a measurable benefit and which individuals would benefit. Currently, it seems likely that methods that reduce exposure to tobacco constituents to the greatest extent would likely provide the greatest benefit, but this remains to be proven .

A systematic and thorough assessment of PREPs and cancer risk will require analysis of data obtained from well-designed laboratory and human studies. In laboratory animals, the shape of the dose–response curves differs for different tobacco constituents, indicating that the dose–response relationship of tobacco smoke is complex.

Dose–Response Relationship

In humans, the carcinogenic response increases most around 5 cigarettes per day, and that there is relatively little increase in carcinogenicity above 20 cigarettes a day. However, while there are sufficient data to conclude that a dose–response relationship exists for the use of tobacco products and cancer risk, the precise dose-response relationship is really not known in part because exposure is not accurately measured without considering actual smoking behavior. There is some evidence to indicate that when internal exposure is considered through biomarkers, the shape of the curve follows a quadratic equation, indicating a greater benefit in exposure reduction for persons who smoke more. Thus, data are insufficient to predict the harm reducing effect of a change from any intensity of smoking to a PREP. There are sufficient data to suggest that dose–response relationships differ as a function of gender, race, age, and ethnicity, although the actual risk levels have not been sufficiently defined to draw definitive conclusions about risks among groups . Based on these types of data and possible modifiers of cancer risk (e.g., genetic susceptibilities, diet, life-style, occupation), it is likely that PREPs would affect risk differently in different people and not at all in some.

There is no evidence of a threshold below which tobacco smoking does not increase cancer risk . This conclusion is consistent with the fact that there are many carcinogens in tobacco smoke, and the aggregate might increase risk at any level. Modeling for low-dose exposures indicates that there is an increased risk with less than one cigarette per day. Thus, persons who initiate smoking with harm reduction products that contain tobacco would be likely to have an increased risk for cancer, and there is unlikely to be a "safe" cigarette. Former smokers who resume smoking with such products would increase their risk further.

Regression of risk using PREPs might eventually bring a smoker to a risk equal to some lower level of lifetime exposure to conventional products. However, there are insufficient data to validate this assumption or indicate that a decrease in risk would be measurable for some or all smokers. There are insufficient data to indicate the shape of the curve for regression of risk for any PREP.

The data are sufficient to conclude, with some caveats, that filtered cigarettes compared to nonfiltered cigarettes pose a lower risk of lung cancer and possibly other cancers. The caveats are that this occurs only in persons who do not substantially increase the number of cigarettes they smoke per day or otherwise compensate by their smoking behavior for lower levels of nicotine. Also, these studies may be confounded by diet, life-style, or other characteristics of people who use filtered cigarettes, which might be different in smokers of filtered compared to nonfil-

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tered cigarettes. The available data are suggestive, but not sufficient, to conclude that smokers of low-tar cigarettes have a lower cancer risk compared to smokers of higher-tar cigarettes, with the same caveats as for the filter smoking studies. However, there are insufficient data to assess the differences in risk for ultralow-, low-, and high-tar cigarettes that are filtered. These cigarettes only became available more recently, so there has not been a long enough latency period in the general population to assess them until recently. There are insufficient data to adequately consider how risk changes when switching types of cigarettes.

This report has not reviewed potential cancer risks due to fibers released from cigarette filters or tobacco additives, because it is thought that the risk of these exposures are substantially lower than the risk from the constituents of tobacco smoke. However, there are no existing data to prove this assumption. Importantly, as harm reduction products are developed that substantially reduce exposure to tobacco constituents, the relative role of fibers and additives in carcinogenesis might become more important. Thus, fiber and additive exposure should be considered when assessing PREPs.

Utility in a Preclinical Setting

There are some experimental models (e.g., in vitro cell cultures, laboratory animals) that may be useful for the assessment of the carcinogenicity of tobacco-related PREPs. Although there are many reasonable models with which to assess individual tobacco smoke products, better models are needed for assessing exposures to complex mixtures. Such studies are not alone sufficient to support claims of potential harm reduction. No claim of potential harm reduction should be allowed without adequate human clinical and epidemiological studies. In vitro and animal studies, however, are very important for (1) determining those products that are not likely to result in measurable harm reduction (e.g., if the product results in exposures that increase genotoxicity), there would be less enthusiasm for it and so should not be tested in a human clinical study and should not be introduced into the marketplace; (2) identifying unforeseen reactions (e.g., if a product reduces exposure but does not decrease tumors), then there might be some constituent or combination of constituents that is either new or more important that those changed in the product); (3) providing supportive evidence for the use of a particular bioassay in humans (e.g., if a biomarker predicts cancer risk in experimental animals); and 4) assessing the dose–response and the shape of the regression of risk for the PREP as exposure is reduced, although the data should be considered qualitative or semiquantitative and cannot be extrapolated directly to human smoking risk. Both in vitro cell culture and experimental animal studies should be used in assessing PREPs, where both can assess genotoxic and nongenotoxic end points, and chronic animal bioassays are needed to assess the end point of cancer risk. It is beyond the scope of the committee to recommend the specific panel of assays, but such a panel will need to be developed. Also, these studies should assess changes due to both specific carcinogens and to complex mixtures, where the latter should be mandatory.

Clinical Assessment of Tobacco-Related Disease and Biomarkers of Tobacco-Related Disease

There is sufficient evidence to conclude that human experimental studies and short-term clinical studies provide evidence of the harmful effects of tobacco products. Thus, such studies can be used in assessing harm reduction. These studies, through the use of biomarkers and surrogate indicators of cancer risk, can evaluate the manipulation of carcinogens and nicotine to re-

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nicotine impairs endothelial function, a property it shares with cigarette smoking, raise questions about its effect on atherogenesis during long-term use (Chalon et al., 2000; Sabha et al., 2000; Gairola and Daugherty, 1999). Such an effect may take many years to emerge and highlights the importance of continued postmarketing surveillance of NRT. Although existing data do not suggest that nicotine is carcinogenic in humans, it would be prudent to have continued surveillance of the incidence of cancer among users of NRT.

Studies of long-term nicotine administration on surrogate variables that more closely resemble the mechanism under consideration (e.g., imaging of plaque progression) and attendant studies in animal models seem timely. Increasingly, the application of genomic and proteomic approaches will help clarify the differential effects of smoking and NRT on the expression and translation of genes related to the development of smoking-related diseases. Finally, the understanding of nicotine's effect on inflammation and the immune response is confused and limited (Sopori et al., 1998). More research is needed to clarify its effects on cytokine generation, the formation of nitric oxide (NO) and eicosanoids, and oxidative injury. Research should continue to explore other potential therapeutic efficacies of NRT, including for ulcerative colitis, analgesia, weight reduction, Parkinson's disease, and cognitive disorders associated with aging and schizophrenia.

The continued use of NRT in conjunction with continued, albeit reduced, smoking prompts additional questions. For example, the constituents of cigarette smoke that mediate tissue injury are not all precisely known, and it is also not known if modulating the coincident nicotine level might influence their absorption, metabolic disposition, mechanism of action, or elimination. Design of such studies will rely upon the development of more refined and tractable methodology to investigate the in vivo kinetics and dynamics of other constituents of cigarette smoke and their interactions with nicotine.

Finally, although ethnicity has been shown to be relevant (Sabha et al., 2000), the factors, that determine interindividual differences in nicotine efficacy, safety, and addictive potential remain largely unexplored. Particular attention might be paid to genetic variation in proteins relevant to nicotine pharmacokinetics and dynamics and their interaction with environmental variables. As with other drugs, one anticipates increasing individualization of nicotine dosage and/or delivery when given as a therapeutic agent. Insight into the interaction of genetic and environmental factors which influence initiation (Gynther et al., 1999; Heath et al., 1999) of cigarette smoking, latency until the practice becomes habitual (Stallings et al., 1999), and the quantity that is then smoked (Koopmans et al., 1999) has been increasing. Clarification of how these factors interact is also likely to afford insights of value in predicting the individual likelihood of response to the use NRT as a strategy for quitting or reducing tobacco exposure.

CANCER (SEE SECTION II, CHAPTER 12)

Feasibility of Harm Reduction in Therapy

There are sufficient laboratory and human data to suggest that harm reduction for cancer might be an achievable goal for persons who cannot stop smoking . There is evidence of decreased risk of cancer for persons who abstain from smoking, and there is strong evidence of a positive relationship between smoking and risk of developing cancer. The risk varies by the different tobacco products used and how they are used. Clearly, abstinence from smoking is the most effective method for reducing cancer risk, and the cancer risk to former smokers is the lowest-level risk that might occur from the use of any PREP. Importantly, it must be recognized that

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harm reduction products would be introduced. Importantly, the use of intermediate markers does not replace long-term follow-up and epidemiological surveillance, but it can be a basis for estimating effects before direct evidence from epidemiological studies is available.

Biomarkers of internal exposure, biologically effective dose, or potential harm have been validated to different degrees. It is typically easier to show a relationship between external exposure and biomarkers in the following order: internal exposure, biologically effective dose, and harm. Conversely, it is typically easier to show a relationship between disease outcome and biomarkers in the following order: harm, biologically effective dose, and internal exposure. It might be acceptable to rely on external exposure measurements for considering risk and dose–response, but only with substantial corroborative biomarker data. The best strategy for assessing the claims of risk reduction methods is to have several markers that range from exposure to outcome, one being linked to another, and at least one with which a dose–response risk assessment can be made.

The recommendation that PREPs be assessed by the use of biomarkers should reflect the available data, which show that individual use and response to tobacco products are affected by cultural and heritable traits. To achieve the greatest confidence that a PREP will reduce risks for persons who cannot stop smoking, well-validated methods for predicting risk, including external exposure indicators, and the best available biomarker assays should be used.

NICOTINE PHARMACOLOGY (SEE SECTION II, CHAPTER 9)

Nicotine is the addictive component of tobacco products, and the strength of this addiction affects the individual's ability to stop smoking (USDHHS, 1988). Nicotine is also a component of most PREPs, and therefore, evaluation of the harm reduction potential of PREPs requires evaluation of nicotine's relative toxicity, especially during long-term use (see Chapter 4).

Structurally, nicotine is very similar to acetylcholine (Ach) and interacts with specific nicotinic receptors (nAchRs) in the central and peripheral nervous systems. The interaction between nicotine and its receptor affects the release of numerous neurotransmitters and results in upregulation of the nicotinic receptors leading to the physiological, cognitive, and sensory effects associated with tobacco use, addiction, and withdrawal. Nicotine also has well-documented effects on metabolism and on the cardiovascular, gastrointestinal, and hormonal systems (see Chapter 9).

Pharmacological nicotine replacement therapy (NRT) has proven to be a remarkably well-tolerated and effective strategy for many, leading to cessation of cigarette smoking at least in the short to medium term (Fiore et al., 2000; Benowitz et al., 1998). Although the experience is much more limited, it is also a potential strategy for reducing the number of cigarettes smoked by smokers who cannot or will not quit (Shiffman et al., 1998; Transdermal Nicotine Study Group, 1991; Rennard et al., 1990; Fagerstrom et al., 1997).

There are important considerations in evaluating nicotine products for possible tobacco harm reduction. First, nicotine is addictive, and although the daily exposure may be reduced by NRT use, continued usage implies psychological dependence, if not physical addiction. It is arguable whether this should be a concern, given the assumption of an undisputed reduction of risk compared to smoking. However, it would seem reasonable to include surveillance of the dependency potential and abuse liability of each NRT product. Furthermore, the effects of long-term nicotine intake on such factors as drug and alcohol consumption, the progression of coincidental diseases, the impact of aging on cognitive and other physiological functions, and susceptibility to other forms of addictive behavior are largely unknown. For example, observations suggesting that

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diate biomarker of cancer risk. Thus, different types of biomarkers along the pathway from internal exposure, biologically effective dose, and potential harm are needed, and additional research is necessary to identify the best combination of markers to be used. Experimental toxicity testing (in vitro and animal models) are not sufficient to support a PREP claim because only validated biomarkers can show that the PREP reduces exposure adequately enough to imply risk reduction. The use of intermediate biomarkers as surrogate risk factors for disease may possibly overestimate the number of people who actually develop disease, because not all early changes in morphology or function progress to disease. On the other hand, it may underestimate if, as expected, other mechanisms are involved in the disease process that are not reflected by the biomarkers. Biomarkers may also underestimate the incidence of disease since none are necessarily present in all who develop disease. Therefore, the implication of potential benefit from a harm reduction strategy could be an overestimate or an underestimate, but this limitation in the scientific methodology for identifying sufficiently specific biomarkers of risk requires acceptance at the current time.

Previously, the most common way to infer exposure reduction (e.g., through use of low-tar cigarettes) has been via methods that simulate human smoking behavior, such as the Federal Trade Commission (FTC) method. Although they provide a standardized way to assess cigarettes, it is clear that these methods have limited usefulness because people smoke cigarettes differently from the machine, with resultant qualitative and quantitative differences in exposure.

Biomarkers may be shown to reveal differences in individual susceptibilities and differences in response depending on dose. Thus, biomarkers that measure both complex exposures and single tobacco product constituents are needed and should be assessed for the range of possible human exposures, and those that assess complex exposures should carry a greater weight. Also, some biomarkers or sets of biomarkers should be developed that reflect exposure to many tobacco constituents in order to monitor for the introduction of new hazards from PREPs.

Today, there remain technical limitations to the use of biomarkers. Depending on the harmful effect, surrogate assays that represent effects in target organs may be easier to perform in humans because the target tissues might not be easily accessible. However, if such is the case, the relevance of the surrogate biomarker to the target organ effect should be demonstrated.

The use of a biomarker for harm reduction assessments should include several qualities including reflection of disease pathogenesis, specificity, and sensitivity. Also, consideration must be given to available harm and harm regression dose–response data, target tissue effects, and validation methods. Each biomarker should be validated for its relationship to exposure and harm, and also as a laboratory assay that provides reliable and reproducible data. Separately, the way interindividual variation in response and smoking behavior affects biomarkers should also be considered.

The assessment of harm and harm reduction should be made through direct human experience, as these products are used by the general population. Most of what is known about harmful tobacco products has resulted from epidemiology and supported by in vitro studies, laboratory animal studies, and human experiments. However, although epidemiological studies can provide the most definitive data about tobacco harm and harm reduction products, the study of diseases with long latency (e.g., cancer, heart disease, COPD) is problematic because such studies often require many years before they provide useful data. Thus, because definitive evidence that a new PREP actually reduces harm will often be unavailable, short-term markers that reflect long-term outcomes are needed. If assessment of the harm reduction potential of a PREP were based only on epidemiological data measuring disease outcome prior to its use by the public, very few if any

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Table 5-3 Exposure and Biomarker Assessment Definitions	
Exposure or Biomarker Assessment[a]	**Definition**
External Exposure Marker	A tobacco constituent or product that may reach or is at the portal of entry to the body
Biomarker of Exposure	A tobacco constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose
Biologically Effective Dose (BED)	The amount that a tobacco constituent or metabolite binds to or alters a macromolecule; estimates of the BED might be performed in surrogate tissues
Biomarker of Potential Harm	A measurement of an effect due to exposure; these include early biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm; also includes "preclinical changes"
[a]Categories and definitions reflect concept that the critical exposure is at the level of a biological macromolecule, so that exposure for this discussion is not limited to a measurement at the portal of entry to the body.	

The latter three measurements in Table 5-3 improve upon the first by quantifying exposure at the cellular level to characterize low-dose exposures or low-risk populations, provide a relative contribution of individual chemical carcinogens from complex mixtures (e.g., tobacco-specific *N*-nitrosamines in cigarette smoke), and estimate total burden of a particular exposure where there are many sources (e.g., benzo[*a*]pyrene [BaP] from air, tobacco, diet, and occupation) (Vineis and Porta, 1996). In assessing PREPs through biomarkers, understanding the biological effects of a wide range of exposures will be important. Within the context of this discussion, exposure at the level of the cell and critical macromolecules is considered with greater weight, rather than the traditional view of exposure at the portal of entry into a person.

Markers of external exposure attempt to measure the dose of tobacco or tobacco smoke constituents that may enter the body and usually involve machine testing of products and user questionnaires. Internal exposure markers assess the amount of tobacco or tobacco smoke constituents or their metabolites in body fluids or organs. Biomarkers estimating the biologically effective dose measure the internal dose that interacts with cells and macromolecules and may be mechanistically related to disease outcome. Finally, biomarkers of potential harm reflect changes in cells and macromolecules that may lead to disease (see Table 5-4).

Measuring the number of cigarettes per day and smoking duration, estimating lifetime exposure, smoking topography, and so forth can provide an effective indicator of exposure that has been associated with harm. However, these measures may be insensitive to changes in risk, are difficult to assess accurately over time, and have not been tested in the context of harm reduction. Also, because there is interindividual variation in the way the body responds to these exposures, such measures might not be sufficiently accurate for new products intended to decrease exposure. Thus, for new products, the relationship of external exposure markers to disease risk might be less predictable. Currently, there is sufficient evidence to show that biomarkers can provide better estimates of risk in the context of exposure, and therefore they will likely be able to provide improved assessments for harm reduction products. However, no single biomarker has been sufficiently validated and related to disease risk that it can be recommended as an interme-

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The remainder of this chapter provides a summary of the major conclusions and recommendations, arranged by chapter, reached by the committee in Section II of this report.

TOBACCO SMOKE AND TOXICOLOGY (SEE SECTION II, CHAPTER 10)

Mainstream tobacco smoke and environmental tobacco smoke each is a complex mixture of toxicants composed of carcinogens and other chemicals with health effects that alone or in combination are only partially known (see Table 5-2) (Davis and Nielson, 1999). The evaluation of conventional tobacco products and tobacco-related PREPs is complicated by a lack of adequate in vivo models of tobacco-related morbidities in man.

Table 5-2 List of Selected Tobacco Mutagens and Carcinogens[a]

Constituent Class	Phase	IARC Evaluation[b]	Examples
N-Nitrosamines	Particulate	Sufficient in animals	Tobacco-specific nitrosamines (NNK, NNN), dimethylnitrosamine, diethylnitrosamine
Polycyclic aromatic hydrocarbons	Particulate	Probable in humans	Benzo[*a*]pyrene,benzo[*a*]anthracene, benzo[*b*]fluoranthene, 5-methylchrysene
Aryl aromatic amines	Particulate	Sufficient in humans	4-Aminobiphenyl, 2-toluidine, 2-naphthylamine
Heterocyclic amines	Particulate	Probable in humans	2-Amino-3-methylimidazo[*4,5-b*]quinolone (IQ)
Organic solvents	Vapor	Sufficient in humans	Benzene, methanol, toluene, styrene
Aldehydes	Vapor	Limited in humans	Acetaldehyde, formaldehyde
Volatile organic compounds	Vapor	Probable	1,3-Butadiene, isoprene
Inorganic compounds	Particulate	Sufficient in humans	Arsenic, nickel, chromium, polonium-210

NOTE: NNK = N-nitrosonornicotine; NNN = nicotine-derived nitroketone.

[a]This list is intended to provide a conceptual overview of the complexity of tobacco product exposures. It is not all-inclusive but is presented to allow the reader to understand the number of considerations that must be made in assessing harm reduction strategies.

[b] International Agency for Research on Cancer: The classifications here refer to evaluations of the compound from any exposure, not just tobacco. Not all chemicals within the class are considered carcinogenic in humans. There is no consideration in this table to delivered dose or route of exposure.

Toxicology studies, both in vitro and in vivo, provide the opportunity to evaluate the potential harm reduction offered by potential reduced-exposure products (PREPs). The comparative potency of the PREP can be determined in a series of pre-clinical studies that include both the PREP and the standard tobacco product that can be replaced by the PREP. The pre-clinical tests should include in vitro tests in both animal and human cells to determine the cytotoxicity and the genotoxicity of the tobacco product to which humans will be exposed. Such tests have recently been reported for a new tobacco-related PREP (Eclipse Expert Panel, 2000). Such a test must include dose–response studies to determine the amount of the exposure material required to cause toxicity. Next, studies should be conducted in vivo in the best animal models available to determine the comparative potency of the PREP versus the standard product in producing: (1) pulmonary inflammation, (2) COPD, (3) cardiovascular disease, (4) reproductive toxicology, and (5) pulmonary neoplasms.

In vitro studies and in vivo animal studies are useful but limited tools in evaluating the toxicity of products that claim to reduce exposure to tobacco toxicants and potentially reduce tobacco-related harm. In vitro studies may allow rapid, low-cost screening for the toxic properties of con-

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ventional tobacco products and tobacco-related PREPs, although the relationship between in vitro toxicity and in vivo human response has not been established for most compounds. These assays include cytotoxicity and genotoxicity assays, which are possible screens for the carcinogenic or inflammatory potential of products. In vivo toxicity testing can be developed to supplement in vitro and clinical studies.

Such animal models, if developed, may be useful as a screening assessment of the efficacy of PREPs for reduction of various tobacco-attributable diseases (see Chapters 12-16). The committee concludes that animal models should be used to test for the potential adverse health effects of tobacco smoke or any proposed additives. The A/J mouse model, which is sensitive to induction of lung adenomas, shows promise as an animal model for screening the potential of tobacco products to induce lung tumors (Witschi et al., 2000; Witschi et al., 1999; Witschi et al., 1997a,b). Future studies should validate the model. These studies (Witschi et al., 2000) indicated that removal of single classes of carcinogens, such as nitrosamine or polycyclic aromatic hydrocarbons (PAHs) may not be protective against induction of lung tumors by smoke. Studies also indicate that some animal models show promise for use in studying the development of symptoms similar to those of chronic obstructive pulmonary disease (COPD), the development of cardiovascular disease, adverse effects on the immune system, intrauterine growth retardation, and poor fetal lung maturation from the inhalation of new or existing tobacco products (see Chapter 10).

Testing the general toxicity of smokeless tobacco and evaluating of the potential harm reduction properties of smokeless tobacco (e.g. Swedish snus) use in smokers may greatly benefit from assays for genotoxic and cytotoxic potential and the animal models discussed above.

Details to be considered in determining the specific set of toxicity tests include species and strain of test animal, duration of test, end points of interest, dose–response considerations, biomarkers of dosimetry and response, and standard comparison products to be tested as positive and negative controls.

EXPOSURE AND BIOMARKER ASSESSMENT IN HUMANS (SEE SECTION II, CHAPTER 11)

Accurate measures of exposure and the development of biomarkers of adequate specificity and sensitivity are needed to evaluate the toxicity and harm reduction potential of PREPs. Biomarkers can be defined as measurements of tobacco constituents, tobacco smoke constituents, or changes in body fluids (including exhaled air) and organs. The assessment of a PREP will have to include markers of external exposure and biomarkers indicative of internal exposure, biologically effective dose (Perera, 1987), and potential harm. The definitions of each are provided in Table 5-3. There have been different definitions of types of exposure assessments used previously, but more recent understandings of biomarker uses and limitations, as well as different approaches needed for PREP evaluation lead to a need for clarification and redefinition.

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Table 5-1 Tobacco and PREP Risk Assessment

	Hazard Identification	Dose Response	Exposure Assessment	Risk Characterization	Risk Management
1983 "Red Book"	Epidemiology Animal Bioassay Short term Studies Comparisons of Molecular Structure	Epidemiology Low-dose extrapolation Animal to human extrapolation	Dose to which humans are exposed Dose of special populations Estimation of size of population potentially exposed	Estimate of the magnitude of the public health problem.	A risk-assessment (qualitative or quantitative) may be one of the bases of risk management
Challenges in Risk Assessment of Tobacco	Complex mixture Animal models are limited Constituents and additives are proprietary information	Dose changes for an individual over time Dose of individual toxicants varies over time Exposure at time of disease progression	Changes in smoking topography Complex mixture	For which disease? At which point in smoking history?	FTC regarding advertising
Additional challenges of PREP Risk Assessment	Products will change rapidly with time	Assessing effect of moving backwards on a dose-exposure curve, assuming long-time previous higher exposure	Changing exposure after long-term higher dose exposure Some toxicants could increase	Need models to consider effects on initiation, cessation, and relapse	FDA authority currently exerted only over pharmaceutical PREPs
Committee Charge	#1: Does product decrease exposure to the harmful substances in or produced during use of tobacco?	#2: Is decreased exposure associated with decreased harm to health? #3: Are there useful surrogate indicators of disease that could be used?	#1: Does product decrease exposure?	#4: What are the public health implications? –	#4: What are the public health implications? – or is this another column, risk management
Disease-specific Summary Data (Chapter 5; Section II)	(3) utility of preclinical research to judge feasibility	(1) dose-response data for conventional tobacco products (2) validation and development of biomarkers (4) short-term clinical and epidemiological studies	(2) validation and development of biomarkers (4) short-term clinical and epidemiological studies	(5) long-term epidemiological studies and surveillance	

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In conclusion, the PREP risk assessment process will be challenging because no single definitive study, either human or experimental animal study, would stand up to rigorous scientific scrutiny to be used in such a process. Therefore, today, several types of data will be needed that includes both experimental animal studies and human clinical data, with a definitive plan to conduct epidemiological and surveillance studies. The clinical data is needed because animal studies cannot predict interindividual differences in human behavior that would affect how the PREP is used or cause damage, and because there are too many uncertainties about the use of animal data. During this interim time, and with more research, the regulatory process might be able to identify key types of data needed for the risk assessment process. At this point in time, however, it can only be concluded that both experimental animal and clinical human studies would be needed, and that this would include both the consideration of exposure to individual PREP constituents and as a complex mixture. It is conceivable that the PREP risk assessment process can be simplified, for example by comparing only experimental data for one PREP to another, but this will require substantial experience and characterizing the data for existing PREPs. Sufficient data for streamlining this process in not available today.

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For *risk characterization,* the questions include:

- Can the exposure levels of the PREP, given its dose–response characteristics, be expected to result in reduced risk of one or more tobacco-related diseases than the standard tobacco product to which it is compared?
- What is the magnitude of any reduction in risk?
- What are the limits in understanding of the risk reduction?
- Do fewer tobacco users quit and use PREPs instead?
- Do former tobacco users relapse to PREPs?
- Do non-users initiate tobacco use through PREPs?

In order to achieve a level of confidence that a PREP will provide meaningful reductions in risk, especially compared to the real possibility of others using this product to initiate or resume smoking, prospective epidemiological studies are required. This could be done in a timely manner for some disease endpoints, such as birth outcomes or recurrence of myocardial infarction. For many other diseases associated with tobacco use, however, definitive demonstration of reduced harm will require studies of a long duration. Moreover, it is reasonable to anticipate that the design of PREPs would change rapidly in the coming years so that assessing PREP use will be difficult.

The claim that a PREP will result in a reduction of the risk for harm requires scientific evidence for the validity of that claim. A discussion of the information relevant to hazard identification and dose–response information (the first two elements of risk assessment) is given in Chapter 10. Information on the best means of evaluating exposures is given in Chapter 11. In the case of tobacco products, animal models of adverse health effects have been problematic in the past, but new animal models show promise for being useful (see Chapter 10). There currently no population risk assessment models that mimic the types of predictions hoped for tobacco users who switch to PREPS, and how the public health will be effected by the initiation of PREP use by never and former smokers.

The committee has evaluated the science base regarding the toxic effects of tobacco on the major diseases known to be caused by tobacco exposure (i.e., cancer and diseases of the cardiovascular, pulmonary, reproductive systems). The committee has done so to arrive at summary conclusions regarding the evidence base that would directly feed into a risk assessment paradigm, such as that described above (see Table 5-1). Specifically, the committee has elaborated in each of the major disease-oriented chapters of Section II and summarized later in this chapter the evidence regarding:

1) the dose–response relationship between tobacco smoke and/or constituent exposure and health outcomes,
2) identification and development of surrogate markers for disease,
3) the utility of preclinical research in understanding the potential of PREPs to be harm reducing for the disease under review
4) utility of short-term clinical and epidemiological studies
5) the role of long-term epidemiological studies and surveillance.

The review of preclinical research and the material in Chapter 10 (Toxicology) provide information on hazard identification and, in part, dose–response assessment. The material on surrogate markers for disease is informative for both dose–response assessment and exposure assessment. The review of the short term clinical studies, epidemiology, and surveillance data provide the proof of reduced harm.

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fore of disease progression) that induce different dose–response effects?

- Are the patterns of adverse health effects different from PREPs compared to conventional tobacco products?
- What is the evidence that reduction in exposure to the targeted compounds in the complex mixture or other hazardous material in the PREP will decrease or reverse the development of disease?
- What is the dose-response relationship between the targeted compounds and the disease outcome?
- What quantitatively happens to disease induction if exposures are reduced?
- How much exposure needs to be reduced to result in a measurable benefit?
- Are there individual susceptibilities (age, gender, and genetic makeup. Prior use of tobacco products) that change this dose/response relationship?

Some dose–response information can be obtained from standard pre-clinical animal studies. However, there will be uncertainties in extrapolating from animal data to humans. Additionally, it will be difficult, even in animals, to determine the response to a reduction in dose after a period of higher exposure.

For *exposure assessment*, the questions include:

- Do PREP users compensate differently than users of more conventional 'low-yield' products?
- Do PREP users exclusively use PREPs or do they switch back and forth between PREPs and conventional products?
- How does the PREP change the exposure pattern for the population?
- Does the introduction of the PREPs increase the number of people initiating use of tobacco products or decrease cessation attempts?
- What is the overall balance in exposures (directly and as environmental tobacco smoke) with or without the PREP?

Past experiences with "low-yield" cigarettes containing less tar and nicotine than other products underscore the need to determine internal dosimetry of toxic material entering the body during use of tobacco-related PREPs. The internal dosimetry of the new products can be compared to that of standard products in short term toxicokinetic studies in humans. Biological markers of internal dosimetry of key ingredients can be used when available.

The risk assessment process will need to rely on the use of animal preclinical and human clinical studies, in which biomarkers of exposure and potential harm can be measured. Biomarkers of exposure to tobacco products have been validated, and are in current use. Unfortunately, few specific early indicators of biomarkers have been validated as predictive of later disease development. It is recognized that today, biomarkers of exposure are better validated compared to biomarkers of potential harm, and that it is more feasible to consider exposure reduction in contrast to risk reduction. However, while an assessment of risk reduction through biomarkers will have more uncertainty, these will need to be included in the PREP risk assessment process in order to enhance confidence that there is no worsening risk, in the least.

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